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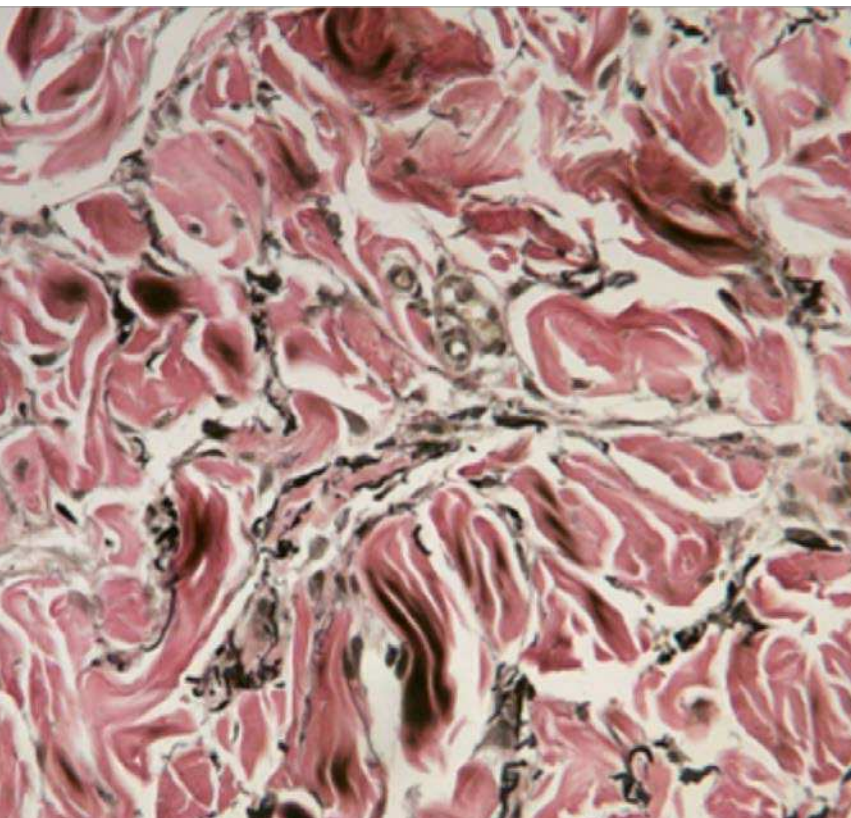
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Anetoderma of prematurity

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Title figure:

Histopathology of anetoderma with fine, fragmented elastic fibers in the dermis (Verhoeff-van Gieson stain) (source: www.anndermatol.org).

Anetoderma (anetos, Greek for relaxed) of prematurity (AOP) is a rare dermatologic disorder characterized by atrophic skin lesions with sharp borders caused by localized loss of elastic fibers. While it seems that the most immature infants are at highest risk for this disease, the precise pathogenesis of the disorder remains to be defined. Because mortality rates of extremely low gestational age neonates (ELGANs) continue to decrease, we expect that AOP will increasingly be seen and health care professionals caring for these patients should be familiar with this disorder.

CASE REPORT 1

This baby girl was born at 24 6/7 weeks of gestation to a G2/P2. The mother had been on metoprolol because of preexisting arterial hypertension. She was admitted to the obstetric ward at 22 4/7 weeks of gestation due to worsening arterial hypertension. At 24 0/7 weeks of gestation, magnesium sulphate infusion for neuroprotection was started and corticosteroids were given for lung maturation. At 24 6/7 weeks of gestation, a Cesarean section was performed due to intrauterine growth restriction, pathologic Doppler signals in the umbilical vessels and progressive pre-eclampsia. Apgar scores were 3, 2, and 5 at 1, 5, and 10 minutes, respectively. Birth weight was 470 g (<P3), birth length 27.5 cm (<P3) and head circumference 21 cm (P5 – 10).

The girl's neonatal course was complicated by very sensitive skin with iatrogenic lesions on abdomen and chest (Fig. 1), ventilator dependence until day of life (DOL) 25, mild bronchopulmonary dysplasia (BPD), surgical closure of the patent ductus arteriosus, coagulase-negative *Staphylococcus* late-onset septicemia (DOL 5), respiratory syncytial virus pneumonitis (DOL 34), and retinopathy of prematurity grade III with plus disease requiring bilateral laser therapy. No abnormalities were observed on cranial ultrasound. The baby was discharged home at 38 0/7 weeks of postmenstrual age (PMA) with a weight of 1860 g (<P3), length of 41.5 cm (<P3) and head circumference of 31 cm (<P3).

Ten weeks after birth, a hypopigmented sharply bordered area on the right side of the trunk was observed for the first time. These lesions occurred in areas where transcutaneous $p\text{CO}_2$ probes, ECG electrodes or disinfectants had been applied. The involved skin area increased in size over time, and the lesions became paler and atrophic. Fig. 2 A–C illustrates the evolution of the skin lesions over a 6-year-period.



Fig. 1

Patient 1 (DOL 11; 26 4/7 weeks PMA): parchment-like skin with ulcerations, dermal hemorrhages and desquamated lesions on abdomen and chest.



Fig. 2

Patient 1: evolution of periumbilical AOP (A: 10th week of life, 36 5/7 weeks PMA; B: 7 months corrected age; C: age 5.5 years).



Fig. 3

Patient 2: extensive skin changes consistent with AOP (A: 17 weeks corrected age; B: 11 months corrected age).

This pregnancy occurred after egg donation in a healthy G4/P2. Up to her emergency admission because of HELLP-syndrome, pregnancy had been uneventful. At 25 3/7 weeks of gestation, a Cesarean section was performed before lung maturation could be completed. The male infant adapted well with Apgar scores of 3, 5, and 7 at 1, 5, and 10 minutes, respectively. His birth weight was 440 g (<P3), birth length 29.5 cm (P3 – 10) and head circumference 21.5 cm (P3 – 10). He was intubated in the delivery room and surfactant was administered.

Invasive and non-invasive respiratory support was necessary for 12 and 49 days, respectively. The neonatal course was complicated by mild BPD, a patent ductus arteriosus (closed with indomethacin), coagulase-negative *Staphylococcus* late-onset septicemia, and *Klebsiella pneumoniae* septicemia with pneumonia and meningitis. The infant was discharged home at 38 0/7 weeks PMA (DOL 89) with a weight of 2350 g (<P3), a length of 44 cm (<P3) and a head circumference of 33 cm (P10).

In the first days of life, his skin was noted to be very fragile and many erosive lesions appeared. At 36 0/7 weeks PMA, a pale, sharply bordered and atrophic area on the abdomen was noted for the first time. Fig. 3 A, B illustrate the evolution of the skin lesions during the first year of life.

CASE REPORT 3

This baby girl was born at 24 2/7 weeks of gestation to a G2/P1. The mother had been admitted two weeks earlier because of preterm labor and vaginal bleeding. At 23 2/7 weeks of gestation, antenatal corticosteroids for lung maturation were administered following rupture of membranes. Because of persistent contractions and fetal bradycardia, a Cesarean section was performed at 24 2/7 weeks. Partial placental abruption was confirmed intraoperatively. Birth weight was 700 g (P50–75), birth length 31 cm (P25–50) and head circumference 21.5 cm (P10–25). The infant was intubated in the delivery room and admitted to the NICU after surfactant administration.

The neonatal course was characterized by prolonged non-invasive positive pressure ventilation, mild BPD, and two episodes of late-onset septicemia possibly due to severe iatrogenic skin lesions (Fig. 4). The girl was discharged home at 37 2/7 weeks PMA with a weight of 2980 g (P10–25), a length of 46.5 cm (P3–10) and a head circumference of 34.5 cm (P50–75). Fig. 5A, B document the evolution of the skin lesions over the first year of life.

**Fig. 4**

Patient 3 (DOL 4; 24 5/7 weeks PMA): intense inflammatory reaction of the skin on chest and upper extremities (left arm: blood pressure device; right arm: ECG electrode), and abdomen (following disinfection prior to insertion of umbilical catheters).

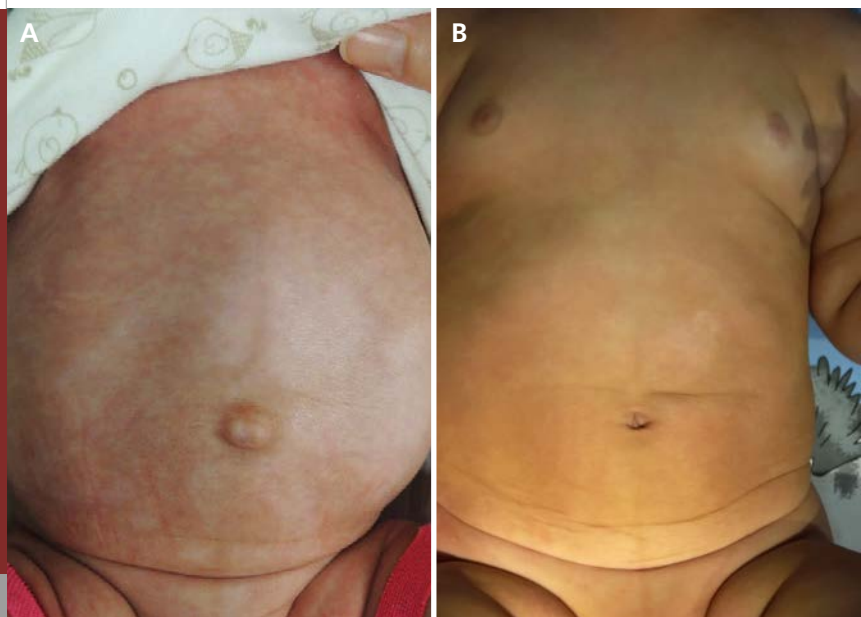


Fig. 5

*Patient 3 (A: 12th week of life; 36 2/7 weeks PMA;
B: 1 year corrected age): sharply bordered translucent
skin areas on the chest and abdomen.*

**Fig. 6**

Patient 4 (16th week corrected age): periumbilical hypopigmented atrophic skin areas.

CASE REPORT 4

This male infant was born at 24 5/7 weeks of gestation to a G2/P1 who had been admitted three days earlier because of preterm labor. Antenatal corticosteroids for lung maturation were given on admission. When signs of chorioamnionitis developed, a Cesarean section was performed. The infant was intubated in the delivery room and surfactant was administered. Birth weight was 870 g (P50–75), birth length was 34.5 cm (P50–75) and head circumference was 23.5 cm (P25–50).

The boy was extubated on DOL 11 and put on non-invasive respiratory support for another 35 days. Apart from conservatively treated meconium plug syndrome and mild BPD, no severe morbidities were observed. He was discharged home at 38 3/7 weeks PMA with a weight of 2680 g (P5–10), a length of 47 cm (P3–10) and a head circumference of 33.5 cm (P10–25).

In this patient, periumbilical atrophic and hypopigmented skin lesion were first observed at 37 1/7 weeks PMA, shortly before discharge from the NICU (Fig. 6).



Fig. 7

Distribution pattern of AOP in ELGAs described in the literature (5) and in the four cases presented in this report.

DISCUSSION

In 1891, Schwenninger and Buzzi were the first to use the term «anetoderma» to describe atrophic skin lesions in adult patients (1). The term referred to sharply bordered and depigmented areas with decreased skin thickness. Frequently, the affected skin runs through a phase of inflammation months before achieving this final stage. Herniation of the structure underlying the skin lesion has been reported. The histopathologic examination of the atrophic skin areas demonstrates isolated perivascular lymphocytic infiltrations in the dermis with a loss of elastic fibers (2).

Anetoderma can occur as a primary, idiopathic disorder (historically subclassified into two types, the Jadassohn-Pellizzari type and the Schweninger-Buzzi type, depending, respectively, on the presence or absence of prior inflammation at the site of the lesion). Secondary anetoderma, on the other hand, has been described in patients with associated diseases, including autoimmune, infectious, and inflammatory conditions, benign and malignant tumors, as well as associated with drugs (i.e., drug-induced) (3).

Following an initial description of permanent skin changes related to transcutaneous oxygen monitoring by Golden in 1981 (4), Prizant et al. were the first to use the term anetoderma to describe atrophic patches in extremely preterm infants (5). They speculated that anetoderma of prematurity (AOP) was due to extreme

prematurity and possibly iatrogenic in origin. Additional reports of AOP have since been published (Table 1) (3–11). The majority of patients with AOP are extremely preterm infants.

The diagnosis of AOP is primarily based on clinical examination and evaluation of the patient's clinical course; histopathology of a skin biopsy is usually not necessary. Over the years, the affected atrophic skin areas grow together with the child, thus the percentage of affected skin remains constant. The lesions have no specific localization, although trunk and extremities seem to be the most frequently affected regions.

While the pathogenesis of AOP is poorly understood, several promotive conditions have been described, favoring the hypothesis of a multifactorial mechanism (Table 2). These conditions can be of physical, toxic or immunologic nature, and are associated with the development of a local dermal inflammatory reaction, responsible for damaging dermal tissue with consecutive loss of elastic fibers.

In the very premature infant, distension of the skin by removing adhesive tape or ECG electrodes can harm its elastic fibers (3, 5, 8, 11). Continuous compression of the skin through prolonged prone position on ECG electrodes or other devices may cause local hypoperfusion with consecutive damage to the der-

Reference		Patients			Comment
Authors	Year	N	GA range	BW range	
Golden SM (4)	1981	2	24–30 weeks	620–1640 g	Hyperpigmented skin craters following prolonged tcpO ₂ monitoring
Prizant TL et al. (5)	1996	9	24–29 weeks	595–1530 g	Affected areas corresponded with placement of monitoring leads or adhesive tape; on biopsy reduction or absence of elastic fibers noted in 4 of 5 patients
Todd DJ (6)	1997	1	32 weeks	795 g	Birth weight (and skin thickness) may be more important than gestational age
Zellman GL, et al. (7)	1997	2	25 weeks	680–780 g	Congenital anetoderma in fraternal twins
Colditz PB, et al. (8)	1999	2	27 weeks	520–630 g	Lesions located on forehead following ECG lead placement for electrical impedance monitoring of cerebral blood volume; growth restricted infants may be particularly vulnerable
Ben-Amitai, et al. (9)	2008	2	26 weeks	1050–1200 g	Anetoderma in premature identical twins
Wain EM, et al. (10)	2008	1	24 weeks	640 g	Congenital anetoderma in surviving twin following feticide of co-twin because of multiple severe congenital anomalies
Goujon E, et al. (11)	2010	11	25–30 weeks	725–1250 g	Anetoderma of prematurity likely results from unnoticed minor iatrogenic trauma (ECG leads, adhesive tape)
Maffei L, et al. (3)	2014	1	24 weeks	470 g	Numerous, localized, round-flat, and atrophic patches of skin on upper chest first noticed between 4th and 5th month of age while in the NICU
Glauser D, et al.	2016	4	24–25 weeks	440–870 g	Case series presented as COTM September 2016

Table 1. Published cases of iatrogenic anetoderma in preterm infants (3–11).

Mechanism	Description
Physical stress	Mechanical distention of the skin (removal of adhesive tape or ECG electrodes) Mechanical pressure (ischemia by pressure of body weight in prone position) Heat stress (transcutaneous pO ₂ /pCO ₂ -device at 42 – 44°C)
Toxic effect	Gel from electrodes or disinfectant solutions
Immunologic mechanism	Allergic reactions (components of electrodes or adhesive tapes) Maternal passive immunity

Table 2. Possible predisposing conditions for the development of AOP.

mal tissue. Cutaneous heat stress by transcutaneous pO_2/pCO_2 -devices (heated up to $44^\circ C$) will also harm the elastic fibers (4). Toxic ingredients which are in contact with the immature skin, for example gel electrodes or disinfectant solutions, could also play a role. Finally, immunologic factors have also been implicated in the pathogenesis of AOP.

Our patients share several features that might have played an important role in the pathogenesis of AOP. They were all ELGANS requiring long-term NICU monitoring. Following admission to our NICU and after periumbilical disinfection with Octenisept®, umbilical catheters were inserted in all four cases. Octenisept® is a colorless disinfectant for skin and mucous membranes. The active ingredient is octenidine dihydrochloride and phenoxyethanol is added as a preserving agent. The minimum exposure time of Octenisept® for skin disinfection is one minute. In animal experiments, no systemic absorption was observed following oral or topical administration. No cutaneous side effects of Octenisept® have been reported, and, according to Swissmedic (12), it may be used in babies and premature infants (without indicating any gestational age limit below which it should not be used). According to our local protocol, the infants were monitored with ECG electrodes, a transcutaneous pO_2/pCO_2 sensor (heated at $42^\circ C$ and placed on the trunk and/or legs) and an oximetry sensor placed on the extremities. No additional monitoring devices were attached to

the infants' skin. Dermal lesions were mainly localized on the trunk, in areas where monitoring devices are often applied, and in the periumbilical region where skin disinfection is used before umbilical catheters are placed (Fig. 7).

As long as the pathogenesis of AOP is unknown, therapeutic options remain symptomatic and prevention of skin damage appears to be essential. Continuous monitoring of vital functions of extremely premature infants in the NICU is unavoidable and skin disinfection is required for many interventions, such as blood sampling or the insertion of intravascular cannulas. Safety precautions for skin care are of utmost importance and should include safe techniques for removal of monitoring devices and adhesive tape. Furthermore, comfortable positioning of the infant to avoid skin compression by the devices is important. Surgical correction of AOP lesions is sometimes required because of herniation of underlying structures or because of aesthetic problems (3).

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